Patient’s Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer

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Keywords
Rectal resection · Postoperative complications · Sarcopenia · Sarcopenic obesity · Radiation attenuation · Muscle mass

Abstract

\textbf{Background/Aims:} To investigate the relation between skeletal muscle measurements (muscle mass, radiation attenuation, and sarcopenic obesity), postoperative morbidity, and survival after treatment of locally advanced rectal cancer.

\textbf{Methods:} This explorative retrospective study identified 99 consecutive patients who underwent neoadjuvant chemoradiation and surgery between January 2007 and May 2012. Skeletal muscle mass was measured as total psoas area and total abdominal muscle area (TAMA) at 3 anatomical levels using the patient’s preoperative computed tomography scan. Radiation attenuation was measured using corresponding mean Hounsfield units for TAMA. Sarcopenic obesity was defined as body mass index above 25 kg·m\textsuperscript{-2} combined with skeletal muscle mass index below the sex-specific median. Postoperative complications were graded by using the Clavien-Dindo classification.

\textbf{Results:} Twenty-five patients (25.3\%) developed a grade 3–5 complication. Lower radiation attenuation was independently associated with overall (\(p = 0.003\)) and grade 3–5 complications (\(p = 0.002\)). Sarcopenic obesity was associated with overall complications (all \(p < 0.05\)). Skeletal muscle measurements and survival were not significantly related.

\textbf{Conclusion:} Radiation attenuation was associated with overall and grade 3–5 postoperative morbidity after neoadjuvant chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications.
Introduction

Treatment of locally advanced rectal cancer consists of administration of neoadjuvant chemoradiation followed by surgery [1]; this treatment method however results in 40% postoperative complication rate [2, 3]. There is increasing evidence that sarcopenia (indicated by low skeletal muscle mass, assessed by measurement of muscle cross-sectional area most often using the computed tomography [CT] scan) is associated with poor clinical outcomes. Sarcopenia is associated with increased infectious complications, prolonged hospital stay, and decreased survival rates following colorectal resection and hepatic resection for colorectal liver metastases [4, 5]. There is also strong evidence to suggest that obesity is a significant risk factor for wound and stoma site complications after colorectal surgery [6]. Combination of sarcopenia and obesity may result in even worse outcomes, since it combines the health risks of obesity and depleted lean muscle mass [7]. Sarcopenic obesity is associated with reduced functional status and survival in patients with solid tumors of respiratory and gastrointestinal tracts [7]. In patients undergoing liver resection for colorectal liver metastasis, sarcopenic obesity was associated with an increased risk of severe postoperative complications compared with patients who did not have sarcopenia [8].

Timely identification of preoperative risk factors for adverse postoperative outcome will help patients and clinicians with treatment decisions, and with the selection of patients who might have a therapeutic window that leaves room for preoperative improvement of their functional health status known to protect from postoperative side effects [9, 10]. The aim of this explorative study was to investigate the relation between skeletal muscle mass, radiation attenuation (expressed in mean Hounsfield Units [HU] for total abdominal muscle area [TAMA]) and sarcopenic obesity, and postoperative morbidity and survival after the administration of neoadjuvant chemoradiation followed by non-laparoscopic resection for rectal cancer.

Method

Patients

A retrospective study was performed including all consecutive patients with locally advanced rectal cancer who were treated with chemoradiation and surgery at our institute between January 2007 and May 2012. This is the same population dataset that we used in a previous article [11]. In the current study, however, we added data of patients’ skeletal muscle mass, radiation attenuation, sarcopenic obesity, and survival.

Patients were included in the study if they had locally advanced rectal cancer (defined as a clinical T4 tumor or T3 tumor with a threatened circumferential margin (CRM ≤ 1 mm) and/or cN2 disease [1]) that was histologically proven with a colonoscopy and biopsy. Patients were excluded if the preoperative abdominal CT scan was missing or if the abdominal CT scan was of poor quality.

Neoadjuvant Chemoradiation and Surgery

Patients underwent a 5-week protocol of concomitant chemoradiation (825 mg·m⁻² capcitabine twice daily) and 3D-conformal radiotherapy (50 Gy in 25 fractions). Operations were carried out by experienced colorectal surgeons according to the total mesorectal excision principle and consisted of abdominoperineal resection, low anterior resection (LAR), or rectal resection with definitive colostomy (Hartmann procedure). The considered optimal interval between chemoradiation and surgery in 2007–2010 was 6 to 8 weeks, from 2010–2011 it was 8 to 10 weeks, and since 2012, it was 10 to 12 weeks.

Outcome Variables

The baseline characteristics included are age (divided in 4 groups based on quartiles), sex, body height, body mass, American Society of Anesthesiologists (ASA) score (I–IV), Charlson comorbidity score, smoking, clinical TNM stage, neoadjuvant chemoradiation regimen, symptoms of obstruction requiring fecal diversion before rectal surgery, interval between the end of chemoradiation and resection, complications of chemoradiation, type of surgery, diverting stoma (only for patients undergoing LAR), operation time, estimated blood loss, blood transfusion intra- or postoperative, pretreatment tumor distance from the anal verge, length of hospital stay, postoperative surgical and general complications, readmission rate, mortality, pathologic tumor response, pathologic TNM stage, completeness of surgical excision (R stage), carcinoembryonic antigen (CEA) level before neoadjuvant chemoradiation, preoperative hemoglobin (Hb), skeletal muscle mass, radiation attenuation, and sarcopenic obesity.

Prespecified definitions were used to score postoperative surgical complications (until 6 months after surgery) [11]. Complications were graded by using the Clavien-Dindo classification (grade 1–5) [12, 13]. An overall complication is a grade 1–5 complication and a grade 3–5 complication is a severe complication. General complications were divided in cardiovascular, pulmonary, renal, or neurological complications.

Survival was defined as overall survival, measured in months from the day of surgery, with a follow-up of 3 years. The electronic patient record system was searched for date of death and/or the general practitioner was contacted.

Muscle Mass Measurements and Definitions

Preoperative CT scans were imported in TeraRecon (TerRecon Aquarius; TeraRecon, USA). Skeletal muscle mass was exploratively measured at 3 levels because in the literature these different levels are used [8, 14, 15]: cross-sections at the third lumbar vertebra (L3) where both transverse processes were visible, and at both the superior and inferior border of the fourth lumbar vertebra (L4). At each level, the cross-sectional
Sarcopenia was defined as skeletal muscle mass index (TPA or TAMA at each level) below the median, calculated for males and females separately (sex specific cut-off value) [20]. Sarcopenic obesity was defined as body mass index (BMI) above 25 kg·m$^{-2}$ combined with skeletal muscle mass index, TPA, or TAMA, below the sex-specific median [20, 21].

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences for Windows (version 22.0; IBM, SPSS Inc., Chicago, IL, USA). Data are presented as mean and standard deviation for continuous normally distributed variables as checked with histograms. For continuous nonparametric variables, median and range were presented. Univariate associations between skeletal muscle mass measurements (TPA, TAMA, and radiation attenuation), sarcopenia, and sarcopenic obesity with overall and grade 3–5 postoperative complications were evaluated for significance, using Fisher exact test or chi$^2$ test for categorical variables and independent t test (if normally distributed) or Mann-Whitney U test for continuous variables. Possible confounders (see baseline characteristics above) were first tested for association with overall and grade 3–5 postoperative complications. In case they were associated with overall or grade 3–5 postoperative complications ($p < 0.150$), they were tested for association with the skeletal muscle mass measurements (TPA, TAMA, and radiation attenuation), sarcopenia, and sarcopenic obesity ($p < 0.150$). The associations between skeletal muscle mass measurements (TPA, TAMA, and radiation attenuation), sarcopenia, and sarcopenic obesity with overall and grade 3–5 postoperative complications were corrected for the remaining potential confounders in a stepwise forward multivariate logistic regression analysis. In case of multicollinearity between variables, the variable that produced the best model fit (based on the −2 log likelihood) was included in the model. Kaplan-Meier estimates and Cox regression analyses were used to assess the association between sarcopenia and sarcopenic obesity with overall survival. All baseline characteristics that were associated with either sarcopenia or sarcopenic obesity ($p < 0.150$) were tested for an association with overall survival. The variables that were also associated with survival were taken into account in the stepwise forward multivariate Cox regression analyses. Statistical significance was determined at $p < 0.05$.

Results

We identified 105 patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiation between January 2007 and May 2012. After exclusion of 6 patients (patients with disease progression, extensive comorbidity, or unresectable tumors), resection of the tumor was performed in 99 patients (96.1%, of which 53, 53.5%, males), with a median age of 66 (range 40–81) years. Sixty-four patients (64.6%) were overweight (BMI ≥25). Eleven patients (11.1%) had a BMI 30–35, and 6 patients (6.1%) had a BMI ≥35. Median (range) muscle index for TAMA at L3 was 52.2 (37.0–70.9) cm$^2$·m$^{-2}$ in men and 39.9 (30.2–75.4) cm$^2$·m$^{-2}$ in women. We were able to retrieve all data of all consecutive patients, except body height and/or body mass ($n = 3$, 3.0%), operation time ($n = 2$, 2.0%), the CEA level before neoadjuvant chemoradiation ($n = 33$, 33.3%), and in 4 patients (4.0%), the skeletal muscle mass/quality could not be measured on one or more levels because of vertebral screws ($n = 1$, 1.0%), poor quality of the CT scan ($n = 1$, 1.0%), or the area of interest was not completely visible on CT scan ($n = 2$, 2.0%). In 2 (2.0%) additional patients, the skeletal muscle mass could not be measured because their body height was unknown.

Of the 99 patients that underwent resection, 68 patients (68.7%) had an overall postoperative complication, of which 43 patients (43.4%) had a grade 1–2 complication and 25 patients (25.3%) a grade 3–5 (severe) complication. An anastomotic leakage was seen in 2 of 18 patients undergoing LAR, a sepsis was seen in 6 of the 99 patients (6.1%), and an abdominal wound complication in 17 of the 99 patients (17.2%). The mortality rate was 2.0% (2 patients). A complete overview of all postoperative complications can be found in Table 3 of our previous study [11] or in online supplementary file 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000490069). The median follow-up after surgery was 32.9 months (interquartile range 19.4–51.1 months). In the univariate relation between demographic and clinical variables and overall postoperative complications, a younger age ($p = 0.017$), an intra- or postoperative blood transfusion ($p = 0.021$), and a longer operation time ($p = 0.093$) were associated with postoperative complications ($p < 0.150$). In the univariate relation between demographic and clinical variables and grade 3–5 postoperative complications, male sex ($p = 0.032$), a higher Charlson comorbidity score ($p = 0.134$), a lower CEA score before chemoradiation ($p = 0.082$), ypT stage ($p = 0.092$), and an intra- or postoperative...
Muscle Measurements in Rectal Resection

In the univariate analysis, sarcopenia was not significantly associated with overall and grade 3–5 postoperative complications. Sarcopenia measured as TPA at L4 superior was the only variable with \( p < 0.150 \) that seemed significantly associated with overall or grade 3–5 complications. Due to multicollinearity between radiation attenuation measurements (L3, L4 inferior, and L4 superior level) and between TPA measurements (L4 inferior and L4 superior), the variable of radiation attenuation and TPA with the best model fit was included in the multivariate logistic regression analysis (radiation attenuation at L3 for both overall and grade 3–5 complications and TPA at L4 superior for grade 3–5 complications).

Of the potential confounders that were assessed for an association with overall postoperative complications, age and operation time were also associated with radiation attenuation and taken into account in the multivariate analysis for postoperative complications. In the final multivariate model (Table 2), lower skeletal muscle radiation attenuation was associated with an increased risk of overall postoperative complications (OR 0.91; 95% CI 0.85–0.97; \( p = 0.003 \)), as was young age (OR 0.92; 95% CI 0.87–0.98; \( p = 0.007 \)).

For postoperative grade 3–5 (severe) complications, TPA at L4 superior and radiation attenuation, as well as the potential confounders sex, Charlson comorbidity score, CEA before chemoradiation, and pathological T (ypT) stage were included in the multivariate analysis. A lower radiation attenuation (OR 0.89; 95% CI 0.83–0.96; \( p = 0.002 \)) and a higher total psoas mass at L4 superior (OR 1.46; 95% CI 1.10–1.94; \( p = 0.009 \)) were associated with an increased risk of grade 3–5 complications (Table 2).

Postoperative Morbidity and Sarcopenia

In the univariate analysis, sarcopenia was not significantly associated with overall or grade 3–5 postoperative complications. Sarcopenia measured as TPA at L4 superior was the only variable with \( p < 0.150 \) that seemed

Table 1. Univariate relation between skeletal muscle mass, radiation attenuation, and postoperative (grade 3–5) complications

<table>
<thead>
<tr>
<th>Radiation attenuation ( a )</th>
<th>Postoperative complication</th>
<th>Grade 3–5 postoperative complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes (( n = 68 ))</td>
<td>no (( n = 31 ))</td>
<td>( p^b ) value</td>
</tr>
<tr>
<td>yes (( n = 25 ))</td>
<td>no (( n = 74 ))</td>
<td>( p^b ) value</td>
</tr>
<tr>
<td>L3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPA</td>
<td>5.3±1.6 (( n = 65 ))</td>
<td>5.5±1.7 (( n = 31 ))</td>
</tr>
<tr>
<td>TAMA</td>
<td>47.1±9.0 (( n = 65 ))</td>
<td>48.5±10.8 (( n = 31 ))</td>
</tr>
<tr>
<td>Radiation attenuation ( a )</td>
<td>34.8±8.7 (( n = 67 ))</td>
<td>39.3±8.3 (( n = 31 ))</td>
</tr>
<tr>
<td>L4 superior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPA</td>
<td>7.2±1.9 (( n = 65 ))</td>
<td>7.5±2.4 (( n = 30 ))</td>
</tr>
<tr>
<td>TAMA</td>
<td>48.5±9.1 (( n = 65 ))</td>
<td>49.5±10.9 (( n = 30 ))</td>
</tr>
<tr>
<td>Radiation attenuation ( a )</td>
<td>35.1±8.8 (( n = 67 ))</td>
<td>39.2±8.0 (( n = 30 ))</td>
</tr>
<tr>
<td>L4 inferior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPA</td>
<td>7.8±2.2 (( n = 64 ))</td>
<td>8.2±2.6 (( n = 29 ))</td>
</tr>
<tr>
<td>TAMA</td>
<td>46.9±9.0 (( n = 64 ))</td>
<td>47.8±11.1 (( n = 29 ))</td>
</tr>
<tr>
<td>Radiation attenuation ( a )</td>
<td>34.7±8.6 (( n = 66 ))</td>
<td>40.6±12.8 (( n = 29 ))</td>
</tr>
</tbody>
</table>

\( a \) Data are presented as mean ± SD.

\( b \) Bold entries are significant (\( p < 0.05 \)).

Radiation attenuation was measured as the mean HU of the total abdominal muscle area at the level of the third lumbar vertebra.

TPA, total psoas area in cm\(^2\) ∙m\(^{-2}\); TAMA, total abdominal muscle area in cm\(^2\) ∙m\(^{-2}\); HU, Hounsfield unit.
to be associated with grade 3–5 complications. However, in the multivariate model, this association was not statistically significant (OR 0.51; 95% CI 0.20–1.29; \( p = 0.152 \)).

**Postoperative Morbidity and Sarcopenic Obesity**

In the univariate analysis, sarcopenic obesity was not significantly associated with overall complications. However, sarcopenic obesity when measured at TPA L4 superior, TAMA L3 and TAMA L4 superior were associated with overall complications with \( p < 0.150 \) and were therefore included in 3 separate multivariate analyses, together with confounders (age and operation time). In the final multivariate models, sarcopenic obesity measured at TPA L4 superior, TAMA L3, and TAMA L4 superior, and young age were significantly associated with postoperative complications (all \( p < 0.05 \); Table 3). Patients with sarcopenic obesity were 3 times more likely (ORs between 3.2 and 3.8) to develop a postoperative complication.

No significant relation was found between sarcopenic obesity and grade 3–5 (severe) complications.

**Table 3. Multivariate relation between sarcopenic obesity and postoperative complications**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3 TAMA</td>
<td>3.77</td>
<td>1.12–12.66</td>
<td>0.032</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.94</td>
<td>0.89–0.99</td>
<td>0.030</td>
</tr>
<tr>
<td>L4 superior TPA</td>
<td>3.21</td>
<td>1.05–9.77</td>
<td>0.040</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.94</td>
<td>0.90–1.00</td>
<td>0.033</td>
</tr>
<tr>
<td>L4 superior TAMA</td>
<td>3.42</td>
<td>1.02–11.42</td>
<td>0.046</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.94</td>
<td>0.90–1.00</td>
<td>0.034</td>
</tr>
</tbody>
</table>

TAMA, total abdominal muscle area in cm\(^2\)∙m\(^{-2}\); TPA, total psoas area in cm\(^2\)∙m\(^{-2}\).

**Overall Survival and Sarcopenia**

In the univariate analysis, sarcopenia at TAMA L4 inferior was the only variable that was associated with overall survival with \( p < 0.150 \) (HR 2.04; 95% CI 0.83–4.99; \( p = 0.152 \)).
0.120). Of all baseline characteristics (see the Method section) that were assessed for an association with overall survival, ASA, BMI, and tumor regression were also associated with sarcopenia at TAMA L4 inferior ($p < 0.150$) and taken into account in the multivariate analysis for overall survival. In the multivariate model, controlled for ASA, BMI, and tumor regression, none of the potential confounders remained in the multivariate model after the stepwise regression. Therefore, the association between sarcopenia at TAMA L4 inferior and survival remained the same.

**Overall Survival and Sarcopenic Obesity**

No significant relation was found between sarcopenic obesity and survival with $p > 0.337$.

**Discussion**

This retrospective study found that a lower skeletal muscle radiation attenuation was associated with overall and grade 3–5 (severe) postoperative morbidity after chemoradiation and resection for rectal cancer. Sarcopenic obesity was associated with overall complications. A few previous studies investigated the influence of skeletal muscle radiation attenuation on postoperative complications following colorectal cancer resection. Sabel et al. [22] showed that lower radiation attenuation was the best predictor of any complication after colectomy for colon cancer. Boer et al. [20] showed that lower radiation attenuation was associated with overall complications after open colon resection for cancer. Body composition might be of key interest to use in predicting outcomes.

More studies investigated the role of sarcopenia on complications after colorectal surgery. Sarcopenia was associated with more infectious complications [5], higher mortality [18], and decreased survival [23] after colorectal cancer resection. Reisinger et al. [24] evaluated whether low muscle mass was associated with increased inflammation after resection of colorectal malignancies by measuring inflammatory markers in plasma. They found that a low muscle mass was associated with an increased postoperative inflammatory response, which may be a part of the explanation for the high incidence of postoperative complications in sarcopenic patients [24]. In the present study, no significant relation between sarcopenia and postoperative complications was found. Sarcopenia is more than only a low skeletal muscle mass measured at a single time point. Sarcopenia is characterized by the loss of skeletal muscle mass, skeletal muscle strength, and/or physical performance [25]. Defining sarcopenia only in terms of muscle mass might be too narrow and may therefore be of limited clinical value [25]. An example is the finding in the present study that patients with a higher muscle mass (TPA at L4 superior) more often had a grade 3–5 complication. Muscle mass might be not depleted in cross-sectional area because of more fat infiltration of the muscle. Fat infiltration is the most widely accepted cause of reduced attenuation of muscle [26]. Measurement of radiation attenuation is potentially a better approach. Future research should investigate if muscle strength measurements of a muscle biopsy (rectus abdominis muscle) correlate with CT measurements.

Sarcopenic obesity could be of higher clinical use than sarcopenia alone. In the present study, sarcopenic obesity was associated with overall complications. Previously, sarcopenic obesity was found to be a predictor for grade 3–5 postoperative complications following open colon cancer surgery [20], and an independent predictor of survival in patients with solid tumors in the respiratory or gastrointestinal tract [7]. After hepatic resection for colorectal liver metastasis, patients with sarcopenic obesity had a more pronounced risk of severe complications compared with patients without sarcopenia (sarcopenic obesity 40% versus non-sarcopenia 8%, $p = 0.02$) [8]. Visser et al. [27] showed that sarcopenic obesity independently increased the risk of postoperative infections in patients undergoing cardiac surgery.

The current study underscores the importance of assessing skeletal muscle mass and quality measurements to select high-risk patients that might benefit from preoperative optimization (prehabilitation) to prevent a dismal course. Studies show that high-risk patients who were placed on a physical exercise training program before major elective surgery, improve their physical fitness [28–30], even after [31] or during [10] neoadjuvant chemoradiation in patients with rectal cancer. It remains to be seen, however, whether improving physical fitness increases skeletal muscle mass, and vice versa. Currently, in our hospital, we perform a randomized controlled trial (www.trialregister.nl, trial registration number NTR4032) to measure the effect of a 3-week prehabilitation program on postoperative complications in high-risk patients who are to undergo colorectal surgery [32], all in accordance with a part of the recent advises of Hulzebos and Van Meeteren [9]. In this trial, the effect of the prehabilitation program on muscle strength will also be investigated.

Since undergoing a CT scan is part of usual care in the work up of all patients with rectal cancer, no additional test is needed to evaluate skeletal muscle mass and radiation attenuation. Skeletal muscle mass and radiation attenuation measurements could potentially be used as a case-mix...
correction factor in the Dutch Surgical Colorectal Audit (DSCA), a quality registration of colorectal surgery in the Netherlands, to make a more accurate comparison of outcome among various hospitals. Future research should reveal optimal skeletal muscle index and quality cutoff points in this specific population. Moreover, it would be of interest to investigate the association between skeletal muscle measurements and oncological outcome and prognosis.

Our study has some limitations. Definitions of sarcopenia and sarcopenic obesity remain under debate. We used definitions based on previous studies [20, 21], which are different than those used in several other studies. A different definition could have led to different results. Moreover, the univariate associations between muscle mass index and outcome, as well as between muscle radiation attenuation and outcome were not calculated for males and females separately, while body composition is not the same between sexes. We used BMI for the definition of sarcopenic obesity based on previous research [7]; however, adipose tissue measurements on the CT scan might be superior to the calculation of BMI. The explorative nature of the skeletal muscle mass analyses at 3 different levels might be both a limitation as well as a strength of our study. For future research, using level L3 might be recommended [33]. But, it remains to be seen whether or not using L3 CT-slices is the best approach. Due to the retrospective and explorative nature of this study, and the limited number of patients, it is subject to potential bias and certain limitations with respect to their internal validity and generalization. Our findings should therefore be interpreted with caution. More research is needed to confirm our results. Since surgery took place between 2007 and 2012, no laparoscopic procedures were performed. Nowadays, to follow a laparoscopic approach is more common and known to result in less complications [34], but the results here may of course only account for non-laparoscopic surgical approaches.

**Conclusion**

In this explorative manuscript, we found that skeletal muscle radiation attenuation was associated with overall and grade 3–5 (severe) postoperative morbidity after chemoradiation and non-laparoscopic resection for rectal cancer. Sarcopenic obesity was associated with overall complications. Skeletal muscle mass and sarcopenia were not associated with postoperative complications. Body composition might be used to identify patients with high risk of worse outcome after surgery, paving the way to select patients that might benefit from preoperative optimization.

**Acknowledgments**

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**Disclosure Statement**

The authors declare that they have no conflicts of interest to disclose.

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